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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/922,240	08/27/97	SCHREIBER S	APV-007.01

HM12/0811

PATENT GROUP
FOLEY HOAG & ELIOT
ONE POST OFFICE SQUARE
BOSTON MA 02109

EXAMINER	
SORBELLO,E	
ART UNIT	**PAPER NUMBER**
1633	14

DATE MAILED: 08/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy.

Office Action Summary	Application No. 08/922,240	Applicant(s) SCHREIBER ET AL.	
	Examiner Eleanor Sorbello	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *14 July 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,29-33,36,38 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,29-33,36,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on July 14, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/922,240 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-27, 29-33,36, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with the scope of the claimed invention, and is repeated for the same reasons of record as set forth in the official action mailed August 3, 1999.

4. Applicant's arguments filed on February 15, 2000 have been fully considered but they are not persuasive.

The claims are directed to a method of inhibiting proliferation of T cells engineered *ex vivo* to express a gene encoding a mutated macrolide binding protein (MBP), the method comprising contacting the T cells with a macrolide, thereby inducing macrolide-dependent inhibition of the proliferation of the T cells.

The term 'macrolide' as defined in 'The Language of Biotechnology-A Dictionary of Terms', second edition-John M. Walker and Michael Cox', as "Any high molecular weight molecule that is not a polymer of smaller subunits of similar chemical type. The term is used to describe a group of antibiotics derived from various strains of *Streptomyces*. They all consist of a macrocyclic lactone ring (12-, 14-, or 16-membered ring) to which novel amino or neutral sugars (eg. Erythromycin) are attached.

In the instant invention, applicant's results indicate an involvement of NF-AT dependent genes, in the regulation of transcription of various cytokines that are involved in cell proliferation, and conclude that that this is the only mechanism by which immunosuppressants function. Applicant's results indicate inhibition of calcineurin/NFAT mediated transcription using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively from *in vitro* experiments only. The only macrolides used in the instant invention are cyclosporin and FK506. However, the Applicant's claims are not limited to cyclosporin and FK506, but encompass all macrolides.

Applicant's argue that *in vitro* results can be correlated to that which occurs *in vivo* . The references cited by applicant have been considered, but have been found to be non-persuasive. Bonini et al.(1997) have presented results of the transfer of HSV-tk gene transfer into donor lymphocytes for the control of allogeneic graft-versus-leukemia and immune reconstitution. However, the results are non conclusive because Bonini et al. profess that their data indicated only a possible increase in efficiency and safety of allo-BMT.

Miller et al. (1995, FASEB, Vol. 9, pg. 190, paragraph 1), in their review pointed out that no single delivery system is likely to be universally appropriate. He stated that the 'For instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer'. Miller therefore alluded to the fact that *in vitro* results cannot be expected to correspond directly to what is expected *in vivo* . Miller concluded that the biggest future challenge lies in vector development where the compromise will be in selecting between level of transcription and the targeting efficiency of vectors. (see pg. 198, col. 1, para 2).

In view of this, the position of record remains that it would require undue experimentation for one skilled in the art to be able to practice the claimed invention of ex vivo gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the lack of guidance set forth in the specification, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

Therefore, for the reasons stated above, the specification is enabled for an in vitro method of inhibiting the calcineurin/NF-AT mediated transcription in T cells using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively.

Claims 32, 33 and 36 are enabled for *in vitro* but remain rejected as the claim language reads on an *in vivo* method.

Conclusion

7. Claims 1-27, 29-33,36, 38 and 39 are rejected.

8. All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600